REMARKS

Status of the Claims

Claims 2, 3, 5 - 13, 26 - 34, and 89 - 98 are pending. Claim 36 is cancelled. The amendment of Claims 2, 26, 29, 83, 90 and 95-97 and the various rejections raised in the Office Action are discussed in more detail below. Amendments made to the claims should not be considered an acquiescence to the Examiner's rejections, but have been made to expedite prosecution. No new matter has been added herewith.

Claim objections

Claim 90 was objected to as appearing to contain a typographical error that was corrected in claim 2 in the previous response. As suggested by the Examiner, applicants have amended claim 90 accordingly.

Rejection Under 35 U.S.C. § 112, First Paragraph: written description

A. Claims 2 - 3, 5 - 13, 26 - 34, 36, 89 - 90 and 93 - 98 are fully supported by the specification.

Claims 2 - 3, 5 - 13, 26 -34, 36, 89 - 90 and 93 - 98 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to be described in the specification. Applicants traverse the rejection.

The Patent Office alleges that new matter was introduced into the claims by the amendments filed on 6/16/06 and maintained the rejection. Applicants respectfully disagree and point to the specification for support.

With regard to claims 2, 89-90 and 95-97, the Examiner argues that paragraphs [0056], [0013], [0072]-[0073] and [0092] do not support the claim amendments because the language includes the term "approximately." However, in addition to the support in these paragraphs, there is direct support for the claim language in the specification on page 6, last paragraph through page 7, first paragraph of the specification which states "Embodiments of the DNA binding region are shown at amino acids 84-147 of the *T. reesei* protein shown in Figure 10, at amino acids 53-116 of the *A. nidulans* protein shown in Figure 10, and at amino acids 45-109 of the *A. niger* protein shown in figure 28."

With regard to claims 26 and 27, Applicants have amended the claims as suggested by the Examiner to specify "*S. cerevisiae*" and *Sch. Pombe*" to expedite prosecution.

With regard to claim 36, Applicants have cancelled the claim to expedite prosecution.

With regard to claim 95, see above for support for the DNA binding domains. Further, the claim has been amended to remove the reference to "combinations" of the proteins to expedite prosecution.

In view of the foregoing amendments and arguments, Applicants submit that the pending claims are described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Accordingly, Applicants request withdrawal of rejection of Claims 2, 26-27, 36, 89-90 and 95-97 under 35 U.S.C. §112, first paragraph.

B. Claims 2 - 3, 5 - 13, 26 - 34, 36, and 89 - 98 are enabled.

Claims 2 - 3, 5 -13, 26 - 34, 36, and 89-98 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants respectfully traverse.

The office action (page 6, last paragraph), states that "the specification, while being enabling for the use of HAC1/hacA isolated from *S. cerevisciae*, *T. reesei*, and *A. niger var. awamori* in a method to increase expression of certain secreted heterologous proteins from yeast, does not reasonably provide enablement for use of any HAC1 UPR-modulating protein comprising a DNA binding domain as set forth in claim 2 or comprising a DNA binding domain with 90%, 95% or even 100% identify with a DNA binding domain set forth in claim 2 in a method to increase secretion of any heterologous protein expressed in any eukaryotic cell." (emphasis added by Applicants). Applicants respectfully disagree. Applicants acknowledge the Patent Office's statement that the specification is enabling for HAC1/hacA isolated from *S. cerevisiae*, *T. reesei*, and *A. niger* var. *awamori* used in conjunction with certain secreted heterologous proteins, but Applicants submit that the specification is also enabling for HAC1/hacA isolated from any fungal cell used in conjunction with secreted heterologous proteins.

> The test for enablement involves identifying whether the experimentation needed to practice the invention is undue or unreasonable (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether any experimentation needed is "undue." These include the breadth of the claims, the state of the prior art, the level of predictability in the art, the amount of direction provided, and the existence of working examples.

Nature of the invention: The Examiner's position is that the invention is complex in that it involves the concurrent heterologous expression of a protein which is secreted and the manipulation of the unfolded protein response such that the secretion of the heterologous protein is increased by increasing the presence of the recited UPR-modulating protein (*See*, Office Action, page 8). The Patent Office states that endogenous increasing the presence of a UPR-modulating protein is not simply a matter of expressing any form of a UPR-modulating protein, for example, HAC1 protein is expressed only after an intron is spliced from the mRNA, relying on the teaching of Shamu, Current Biology: R121-R123 (1998).

The claim has been amended to specify that the heterologous protein is expressed from a fungal cell, thus, the nature of the invention is the expression and secretion of a heterologous protein in a fungal cell by expressing the heterologous protein in the presence of an HAC1 protein. The specific HAC1 proteins to be used are specified using sequence similarity to known fungal HAC1 proteins SEQ ID NO:5, 6, or 19. The skilled artisan is also given the information that these HAC1 genes include mRNA splicing regions and that the splicing regions can interfere with the expression of the HAC1 protein. Methods are described in the specification by which the spliced regions can be identified. Using this information, it is well within the ability of the skilled artisan to remove the spliced regions of a gene for expression in a fungal cell other than the host fungal cell. The skilled artisan would already possess the knowledge of methods of removing introns. In fact, the process of removing the intron is also discussed in paragraph 8 of the specification and Examples 4, 5, 7 and 8. Enough is taught that the skilled artisan could identify a HAC1 gene and how it is processed in order to get an inducing form of the mRNA. In this way, the skilled artisan has the tools and knowledge to be able to express any HAC1 protein from any fungal cell. Further, the process of expressing and secreting heterologous proteins from a fungal cell is a well-known process. Thus, given a fungal cell that is expressing a heterologous protein, it would require some experimentation, but not undue experimentation to express an HAC1 protein as claimed and identify whether the heterologous protein is secreted.

Breadth of the claims: The Examiner's position is that the claims are very broad in that they encompass the secretion of any heterologous protein from any eukaryotic cell as well as the use of any HAC1 UPR-modulating protein isolated from a yeast or filamentous fungi comprising a DNA binding domain that has at least 90% identity to a DNA binding domain of a – c. However, the claim has been amended to specify that the eukaryotic cell is a fungal cell.

The claims already specify that the HAC1 UPR-modulating protein has 90% identity to the DNA binding domain of SEQ ID NOS:5, 6, or 19. The fact that Applicants do not provide examples regarding every HAC1 UPR modulating protein having high identity (90%) with SEQ ID NOS: 5, 6, or 19, does not render the present claims unpatentable. The Specification teaches the DNA and protein sequence of three HAC1 UPR modulating proteins from three different fungi. Techniques were well known in the art on how to compare the protein with other proteins and have a reasonable expectation of success for determining if the protein with the correct sequence identity had UPR-modulating activity (assays are provided in the specification). Beginning with the sequence provided, one of skill in the art would know how to proceed if they wanted to generate variants – compare the sequence with known related sequences with the understanding that little variation is allowable in the claimed DNA binding domains, modifying the nucleic acid sequence encoding the parent HAC1 UPR modulating protein, and identifying whether the variant still has the activity of the parent. All of the techniques were familiar to the skilled artisan or taught in the specification. Thus, the definition of the HAC1 UPR-modulating protein is not overly broad.

Further, while the heterologous protein is not specified, Applicants submit that leaving this aspect of the claim broader is not burdensome. The fact that some experimentation may be needed is not fatal; the issue is whether the amount of experimentation required is 'undue." Id. At 736-737, 8 USPQ2d at 1404. In re Vaeck, 947 F. 2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 19910. Thus, for example, armed with a fungal cell expressing a HAC1 UPR-modulating protein that has been shown to work for a control heterologous protein, it would be a simple process for the skilled artisan to substitute any appropriate heterologous protein for the control to identify whether it is also secreted. Thus, applicants respectfully submit the breadth of the claims is not undue.

Guidance of the specification/the existence of working examples: The Examiner's position is that "The specification teaches that secretion of a heterologous protein can be increased by expression of a UPR inducing form of a HAC1 recombinant nucleic acid. " and that there are three working examples (Example 7, 9 and 12) in the specification - none of which uses eukaryotic cells other than yeast cells. Further, other than α-amylase, chymosin, laccase and preprochymosin, no examples of heterologous proteins, are provided. Further, no examples of HAC1 UPR-modulating proteins except those isolated from *S. cerevisciae, T. reesei*, and *A. niger var. awamori* are provided.

However, applicants submit that the Examples, and the guidance of the specification in combination with the knowledge of the skilled artisan enables one skilled in the art to make and use the invention.

While the examples showing use of heterologous fungal HAC1 genes use a single type of fungal cell, Applicants submit that this cell is used as a representative fungal cell in a process general to fungal cells, just as *E.coli* is often used to experimentally test bacterial expression. Further, there are other examples that show that homologous fungal HAC1 genes increase expression of a heterologous protein in *A. niger* (see Example 12 and 13), and *T. reesei* (Example 9) and there are examples to show that HAC1 genes exist and function comparably in a number of different fungal cell types (Example 4, Example 8).

The HAC1 genes from different fungi show strong sequence identity in the DNA binding consensus regions. For example, the *A. nidulans* HACA gene, the *A. niger* HACA gene and the *T. reesei* HAC1 gene were identified herein by doing a blast search and looking for homology to the DNA binding region of the yeast HAC1 (see Example 3). Thus, four exemplary HAC genes from a variety of fungi are provided, a method to identify other HAC1 genes and the DNA binding consensus region for four exemplary HAC genes from a variety of fungi are also provided. With this information, the skilled artisan can identify HAC genes from other fungi without undue experimentation.

Further, the examples provide strong evidence for the ability to use any fungal HAC1 cDNA in any fungal cell successfully. Example 1 shows the expression of a bacillus protein is increased in a yeast strain using a yeast HAC1 gene. Example 5 shows that yeast HAC1 disruptions can be complemented by a T. reesei HAC1 cDNA. Example 7 shows successful expression of a heterologous protein in yeast using a *Trichoderma* HAC1 cDNA. Example 9 shows that a different heterologous protein works as well.

With respect to the heterologous protein usable in such a system, many heterologous proteins are known that are expressible in fungi. Further, given the general level of skill in the art, it would be routine to prepare a working HAC1 fungal cell and system for screening heterologous proteins. Applicants submit it would not require undue experimentation to identify whether a heterologous protein could be substituted for a control protein in such a system.

Predictability of the art and the amount of experimentation: The Patent Office points to two references Valkonen *et al.* (Applied and Environmental Microbiology 69 (4) 2065-2072, (2003)) and Bowring, et al. to support their position that one of skill in the art would be required to conduct a

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burdensome and undue amount of experimentation to determine which UPR-modulating proteins encompassed by the claims could be used in conjunction with which heterologous proteins in a method to increase heterologous protein secretion in any eukaryotic cell, especially in a mammalian cell.

However, the claims have been amended to specify that the Eukaryotic cell is a fungal cell. As previously stated, the skilled artisan, using the teaching in the specification and their own inherent knowledge could overexpress a heterologous protein using a HAC1 gene as claimed. For example, a strain expressing a control protein could be used to identify which HAC1 gene works best in the fungal cell. After which, different heterologous proteins could be substituted for the control protein. While many of these methods are directly described and taught in the specification, the skilled artisan can supplement any methods that are not taught using the knowledge of expression systems and protein processing in that system.

In view of the foregoing arguments and amendments, Applicants respectfully request withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph.

Conclusion

In light of the above amendments, as well as the remarks, Applicant believes the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7595.

Respectfully submitted,

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